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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,967	09/13/2005	Charlotta All-Ericsson	ON/4-32739A	4092

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,967	ALL-ERICSSON ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2 and 4-7 are presented for examination.

Applicant's Amendment filed January 3, 2008 has been received and entered into the present application.

Claims 1-2 and 4-7 remain pending and under examination. Claims 1-2 and 4-7 are amended and claims 9-10 are cancelled.

Applicant's arguments, filed January 3, 2008, have been fully considered. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 6 is directed to the method of claim 1, directed to a method of treating a mammal suffering from uveal melanoma comprising administering to said mammal in need of such treatment a dose of the claimed compound (or a pharmaceutically acceptable salt thereof), wherein the claimed compound is administered at a daily dose corresponding to 100 mg to 1000 mg of "Compound I free base".

In particular, it is unclear to what compound the phrase "Compound I free base" refers, since any previous reference to "Compound I" is noticeably absent in the claim from which it depends. Specifically, it is unclear as to whether "Compound I" refer back to the compound of claim 1 (i.e., 4-(4-

methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide) or to another compound not specifically stated in the claim(s). As a result, the claim fails to clearly, precisely or deliberately set forth what compound is, in fact, encompassed by the phrase "Compound I" such that one of ordinary skill in the art would have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection.

For these reasons, the claim fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and is, thus, properly rejected.

For the purposes of examination, the phrase "Compound I free base" will be interpreted to refer back to free base of the claimed compound 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman et al. (WO 99/03854; 1999) in light of Mouriaux et al. ("Implication of Stem Cell Factor in the Proliferation of Choroidal Melanocytes", *Exp. Eye Res.*, 2001; 73:151-157), cited to show a fact, in view of Ijland et al. ("Expression of Angiogenic and Immunosuppressive Factors by Uveal Melanoma Cell Lines", *Melanoma Research,* 1999; 9:445-450), each already of record, for the reasons of record set forth at pages 10-13 of the previous Office Action dated July 24, 2007, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Example 1 at p.4 of the instant specification describes the dose response for the treatment of four uveal melanoma cell lines (i.e., OCM-1, OCM-3, 92-1 and mel 202) with the methansulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide. Applicant relies upon the data presented in Table 5 of the specification showing the dose response (as a percentage of living cells) to support the assertion that there is an unexpected result from using this particular compound in uveal melanoma cell lines. Applicant alleges that such unexpected results could not have been predicted.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Initially, it is noted that Applicant has failed to set forth what distinguishes the set of results designated as "1" versus those designated as "2" in the summary Table at p.5 of the instant specification. For the purposes of consideration herein, it is understood to indicate a first assay and a second assay. However, Applicant is requested to provide clarification on this issue since the discussion provided in the Example fails to address the difference between "1" and "2" such that the artisan would have been reasonably apprised of the difference between them.

Applicant alleges that the present invention is non-obvious over the prior art because the use of

the methansulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide demonstrated an unexpected anti-proliferative effect in four uveal melanoma cell lines (OCM-1, OCM-3, UM 92-1 and mel 202) and references the data presented in the Table at p.5 of the instant specification. While such results have been carefully and closely considered, it remains that (1) the compound used in the example was the methansulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide, whereas the presently claimed subject matter is directed to the use of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide or any pharmaceutically acceptable salt thereof, and (2) several of the concentrations of methansulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide, in fact, demonstrated an *increase* in cell proliferation in certain uveal melanoma cell lines and/or failed to demonstrate an *unexpectedly* potent anti-proliferative effect in the cell lines studied, whereas the presently claimed subject matter is directed to the use of *any* dose of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt thereof (note that the claims are not even limited to a "therapeutically effective amount" to treat the claimed disease, but are open to the use of any dose). Furthermore, as evidenced by the data in the Table at p.5 of the specification, it appears that the dose and the amount of time that said dose of the compound is allowed to incubate with the uveal melanoma cells is clearly pertinent to achieving Applicant's allegedly unexpected anti-proliferative effect.

For example, Applicant's attention is directed to the incubation of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide methansulfonate salt with the uveal melanoma cell line mel 202. For each concentration studied (i.e., 0.15, 0.3, 0.6, 1.25, 2.5, 5 and 10 μM) after 24 h incubation with the claimed compound, cell viability did not decrease below 92% for the majority of samples studied (i.e., 0.15, 0.3, 0.6, 2.5 and 5 μM) and only decreased below 92% for

two single samples (i.e., 1.25 μM, which had 83% viability, and 10 μM, which had 78% viability). More importantly, however, following 24 h incubation with the claimed compound in the second study, cell viability actually *increased* with select concentrations [please see, in particular, 0.3 μM (105% viability); 0.6 μM (104% viability); and 5 μM (101% viability)] and did not demonstrate a particularly potent anti-proliferative effect [please see, in particular, 0.15 μM (98% viability); 1.25 μM (95% viability); and 10 μM (87% viability)].

Incubation for 48 h clearly demonstrated a greater anti-proliferative effect over incubation for only 24 h and further supported a trend to increase the anti-proliferative effect with an increase in dose. Please see, e.g., study (1) and (2) in uveal melanoma cell line UM92-1, study (1) and (2) in uveal melanoma cell line OCM-1, and study (1) and (2) in uveal melanoma cell line OCM-3. Studies (1) and (2) in uveal melanoma cell line mel 202 generally supported this trend also, but further demonstrated a considerable amount of fluctuation among the concentrations of compound used. Most importantly, however, it is noted that, at lower concentrations of the compound, the anti-proliferative effect is not necessarily probative of unexpected anti-proliferative activity due to the fact that only 87% or 92% viability was achieved using 0.15 μM of the compound in UM92-1 and only 98% or 73% viability was achieved using the same amount of compound in OCM-1 uveal melanoma cells. In light of this data, it is clear that (1) the incubation time over which the cells are exposed to the compound and (2) the concentration of the compound used for incubation are each essential to attaining any unexpectedly potent anti-proliferative activity, as evidenced by the fact that such an effect is not achieved using simply *any* incubation time or *any* concentration of the active compound.

Though it is noted that the proffered data does perhaps show an unexpected anti-proliferative effect in certain uveal melanoma cell lines using certain concentrations of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide methansulfonate salt and certain incubation time(s) that would not necessarily have been expected from the prior art, it remains

that the proffered results do not provide a basis for concluding that the claimed subject matter would not have been obvious because the results that support an unexpectedly potent anti-proliferative effect are (1) limited solely to the methansulfonate salt of the claimed compound, (2) generally employ at least 48h incubation time for the most potent effect and (3) are generally unexpectedly effective at higher concentrations of the active agent (though this appears dependent upon the cell line to be treated), while the claims subject to this rejection encompass (1) 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide *per se* or any pharmaceutically acceptable salt thereof, (2) *any* therapeutically effective amount of the claimed compound (notably in the absence of any required incubation time), and (3) any type of uveal melanoma. Further, it has not been argued or demonstrated on the record that the results obtained with the exemplified combinations would have been exemplary of the same or substantially similar results that would have been expected to occur over the entire scope of the claimed subject matter.

In this regard, MPEP §2144.08(II)(B) is relied upon and reads, in-part: "When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the Applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness. Id. For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.' *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (**Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the**

probative value thereof.) But see, *In re Grasselli*, 713 F.2d at 743, 218 USPQ at 778 (Evidence of superior properties for sodium containing composition insufficient to establish the non-obviousness of broad claims for a catalyst with 'an alkali metal' where it was well known in the catalyst art that different alkali metals were not interchangeable and Applicant had shown unexpected results only for sodium containing materials); *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) (Evidence of superior properties in one species insufficient to establish the nonobviousness of a subgenus containing hundreds of compounds); *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (one test not sufficient where there was no adequate basis for concluding the other claimed compounds would behave the same way)." (emphasis added)

Here, just as a single point in space fails to define a line, even though the results shown with certain concentrations of the methansulfonate salt of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide following particular incubation times appear to demonstrate an anti-proliferative effect that was both unexpected and unpredictable from the prior art, the results demonstrated for these discrete combinations would be insufficient to establish the non-obviousness of the entirety of the presently claimed combinations (i.e., any therapeutically effective amount of 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)-pyrimidin-2-ylamino)phenyl]-benzamide or any pharmaceutically acceptable salt thereof in the absence of any particular length of incubation with the active compound) absent any concrete evidence or scientifically sound reasoning as to why these other embodiments would have been reasonably expected to demonstrate the same unexpected effect, particularly with using different formulations of the active compound in distinctly different amounts and length of incubation.

Accordingly, while Applicant's data provided in the instant specification has been fully and carefully considered, it remains that Applicant has not provided sufficient evidence and/or explanation to support the allegation that an unexpected effect over the entire scope of the claimed subject matter has

been demonstrated. Furthermore, even though an apparently unexpected effect has been demonstrated for some of the discrete combinations provided in the Example of the instant specification, Applicant has not provided any objective evidence, scientific reasoning or persuasive argument on the record to provide an adequate basis for concluding that such discrete combinations shown were somehow probative of the same (or at least substantially similar) unexpected effect over the entire scope of the claimed invention. In short, the evidence is, respectfully, insufficient to be supportive of nonobviousness on the grounds of an unexpected effect and not commensurate in scope with the claimed subject matter.

Applicant is reminded that should he rely upon unexpected results to patentably distinguish over the prior art, the present claims must be limited to the embodiment(s) which is (are), in fact, unexpected. Note also that Applicant is burdened with the responsibility of explaining why the evidence provided to support secondary considerations is probative of non-obviousness beyond what data is explicitly provided as unexpected. Please see MPEP §716.02(b)[R-2], particularly Section (II), which states, "[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." *Ex parte Ishizaka*, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992). In the instant case, though the instant data was provided in the instant specification and not a declaration, the burden is nonetheless on Applicant to explain the data provided as evidence of non-obviousness of the claimed subject matter.

Moreover, Applicant is reminded that, "The submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987)." In view of this, and further in view of the fact that the provided evidence fails to be commensurate in scope with the claimed subject matter for the reasons *supra*, the totality of the evidence of nonobviousness fails to outweigh the evidence of obviousness as set forth *supra* when all of the evidence is considered. Accordingly, the rejection is properly maintained.

For these reasons, and those previously made of record at pages 10-13 of the Office Action dated July 24, 2007, rejection of claims 1-2 and 4-7 remains proper and is **maintained**.

Conclusion

Rejection of claims 1-2 and 4-7 remains proper and is **maintained**.

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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/Leslie A. Royds/
Patent Examiner, Art Unit 1614

March 17, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614